1,067,203

PATENT SPECIFICATION

NO DRAWINGS

1,067,203

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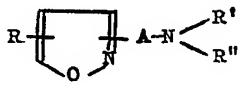
COMPLETE SPECIFICATION

Improvements in or relating to the production of Isoxazole Compounds and the products thereof

We, SHIONOGI & CO. LTD., of 12, 3-chome, Dosho-machi, Higashi-ku, Osaka, Japan, a Japanese Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

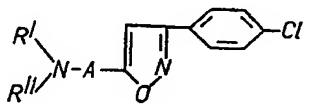
Our copending British Patent Application No. 47065/63 relates to isoxazole compounds and their production, and in the Complete Specification thereof there are described and claimed isoxazole compounds represented by the formula:



wherein R is a substituted or unsubstituted isocyclic or heterocyclic ring, each of R′ and R″ is a hydrogen atom or an aliphatic hydrocarbon residue, or wherein R′ and R″ when taken together with the nitrogen atom represent a heterocyclic group, A is an alkylene group having from 1 to 5 carbon atoms, and wherein one of the groups R and AN< is present at the 3-position and the other at the 5-position, and salts thereof.

In these compounds R may be phenyl substituted with a halogen atom substituent.

According to the present invention, there are provided isoxazole compounds represented by the formula:



wherein each of R′ and R″ is a hydrogen atom or an aliphatic hydrocarbon residue, or wherein R′ and R″ when taken together with the nitrogen atom represent a heterocyclic group and A is an alkylene group having not more than five carbon atoms, and their hydrochlorides.

Specific examples of the isoxazole compounds are as follows:—

3 - (*p* - Chlorophenyl) - 5 - diethylaminomethylisoxazole and its hydrochloride,
3 - (*p* - Chlorophenyl) - 5 - piperidinomethylisoxazole and its hydrochloride,
3 - (*p* - Chlorophenyl) - 5 - morpholinomethylisoxazole and its hydrochloride,
3 - (*p* - Chlorophenyl) - 5 - (2 - dimethylaminoethyl) - isoxazole and its hydrochloride.
3 - (*p* - Chlorophenyl) - 5 - (2 - piperidinoethyl) - isoxazole and its hydrochloride,
3 - (*p* - Chlorophenyl) - 5 - (2 - morpholinoethyl) - isoxazole and its hydrochloride.

The compounds of the present invention are useful as antipyretic, analgesic, antitussive and/or antinflammatory agents. The compounds may be formulated as known *per se*.

The invention includes a pharmaceutical composition comprising an isoxazole compound in accordance with the invention or its hydrochloride salt, and an inert diluent or carrier.

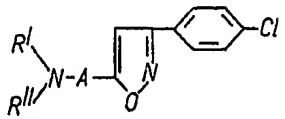
The following Example serves to illustrate the invention:—

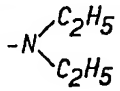
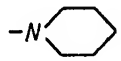
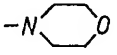
EXAMPLE.

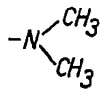
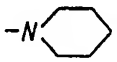
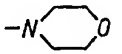
To a solution of 3 - p - chlorophenyl - 5-(2 - chloroethyl) - isoxazole (2.4 g) in toluene (20 ml), there is added dimethylamine (1.5 g), and the resultant solution is heated for 8 hours while refluxing. After cooling the reaction mixture is shaken with dilute hydrochloric acid. The aqueous phase is washed with benzene, made alkaline with 2% sodium hydroxide

solution and shaken with ether. The ether layer is washed with water, dried over anhydrous potassium carbonate and the solvent removed. The resulting liquor is distilled under reduced pressure to give 3 - p - chlorophenyl - 5 - (2-dimethylaminoethyl) - isoxazole (1.9 g) as a colourless oil boiling at 160°C/0.5 mmHg. The hydrochloride has the form of colourless needles melting at 206 to 207°C, when crystallized from ethanol.

In a similar manner, there are produced other isoxazole compounds. Some examples are shown in the following table:

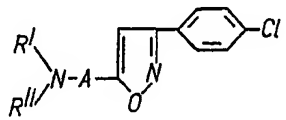


Compound	—A—		Appearance (Melting point or boiling point)	Salts (Melting point)
3-(*p*-Chlorophenyl)-5-diethylamino-methyl-isoxazole	—CH_2—		Liquid (B.P., 145°C/0.1 mmHg.)	Hydrochloride (M.P., 187 to 188°C.)
3-(*p*-Chlorophenyl)-5-piperidino-methyl-isoxazole	—CH_2—		——	Hydrochloride (M.P., 245.5 to 247°C.)
3-(*p*-Chlorophenyl)-5-morpholino-methyl-isoxazole	—CH_2—		——	Hydrochloride (M.P., 240 to 241°C.)

3-(*p*-Chlorophenyl)-5-(2-dimethyl-aminoethyl)-isoxazole	$-(CH_2)_2-$		Liquid (B.P., 160°C/0.5 mmHg.)	Hydrochloride (M.P., 206 to 207°C).
3-(*p*-Chlorophenyl)-5-(2-piperidino-ethyl)-isoxazole	$-(CH_2)_2-$		Crystal (M.P., 74 to 75°C).	Hydrochloride (M.P., 229 to 230°C.)
3-(*p*-Chlorophenyl)-5-(2-morpholino-ethyl)-isoxazole	$-(CH_2)_2-$		Crystal (M.P., 123.5 to 125°C.)	Hydrochloride (M.P., 233 to 235°C.)

WHAT WE CLAIM IS:—

1. An isoxazole compound represented by the formula:



wherein each of R′ and R″ is a hydrogen atom or an aliphatic hydrocarbon residue, or wherein R′ and R″ when taken together with the nitrogen atom represent a heterocyclic group and A is an alkylene group having not more than five carbon atoms, and its hydrochloride.

2. 3 - (p - Chlorophenyl) - 5 - diethylamino-methylisoxazole and its hydrochloride.

3. 3 - (p - Chlorophenyl) - 5 - piperidino-methylisoxazole and its hydrochloride.

4. 3 - (p - Chlorophenyl) - 5 - morpholino-methylisoxazole and its hydrochloride.

5. 3 - (p - Chlorophenyl) - 5 - (2 - dimethyl-aminoethyl) - isoxazole and its hydrochloride.

6. 3 - (p - Chlorophenyl) - 5 - (2 - piperidinoethyl) - isoxazole and its hydrochloride.

7. 3 - (p - Chlorophenyl) - 5 - (2 - morpholinoethyl) - isoxazole and its hydrochloride.

8. A process for preparing isoxazoles and their hydrochlorides substantially as described herein, with reference to the foregoing Example.

9. Isoxazoles and their hydrochlorides when prepared by the process of claim 8.

10. A pharmaceutical composition comprising an isoxazole compound, or its hydrochloride salt as claimed in any one of claims 1 to 7, or claim 9 and an inert diluent or carrier.

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